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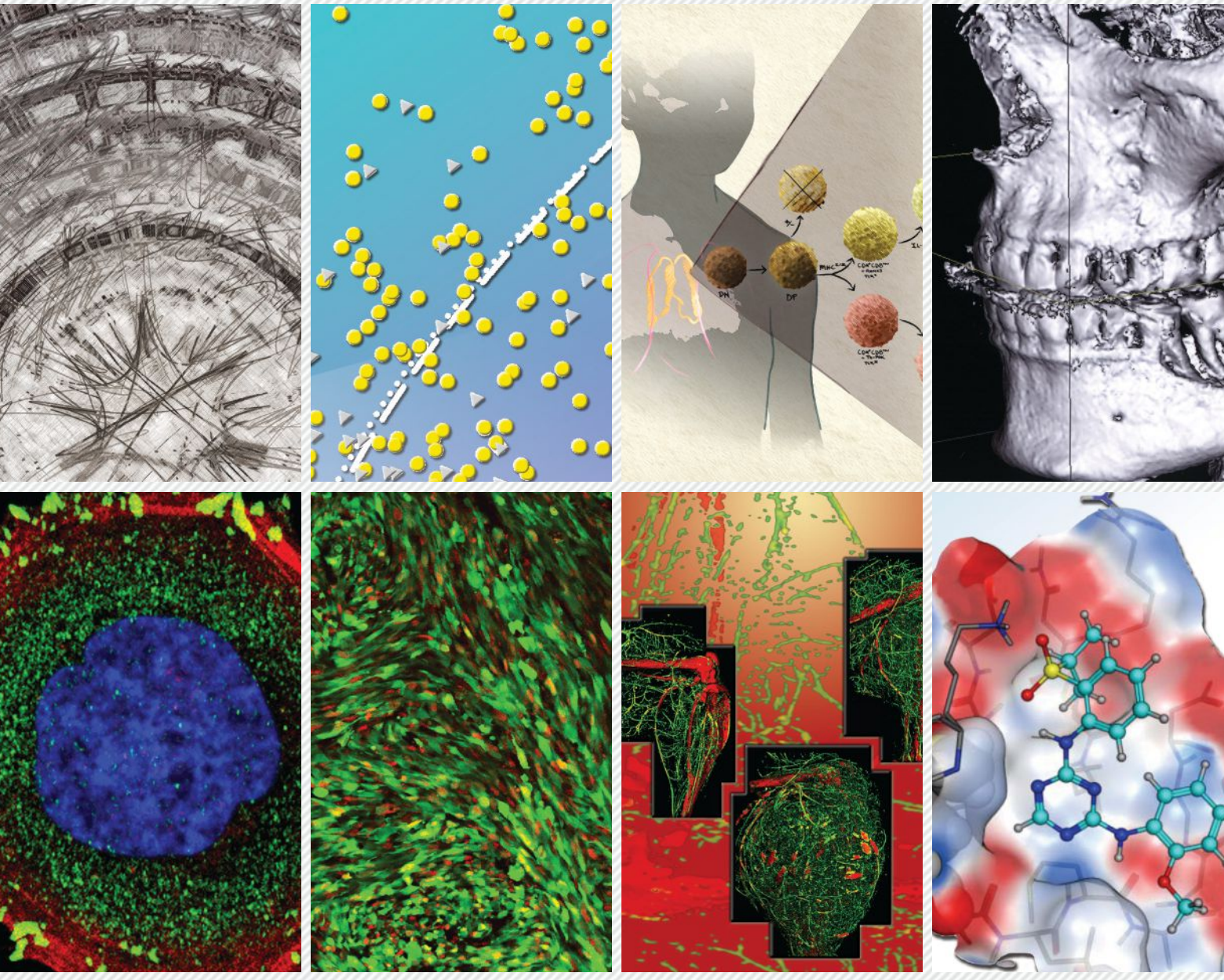

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The Best of the AACR Journals

The AACR is proud to present "The Best of the AACR Journals," a collection of the most-cited articles published in 2014 across the AACR journal portfolio. We congratulate the authors of these outstanding articles for their tireless efforts and contributions to the cancer research field.

Each journal's section in the collection includes the most-cited review article and the four most-cited research articles based on the total number of citations from date of publication through January 2016.

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Cancer Discovery

Lewis C. Cantley, PhD
Editor-in-Chief

José Baselga, MD, PhD
Editor-in-Chief

Scope

Cancer Discovery publishes high-impact, peer-reviewed articles describing major advances in research and clinical trials. As the premier cancer information resource, the Journal also presents Review Articles, Perspectives and Commentaries, News stories, and Research Watch summaries of important journal articles to its readers to keep them informed about the latest findings in the field. Topics span the spectrum of cancer research and medicine from the laboratory to the clinic and epidemiologic studies.

Review Article

Patient-Derived Xenograft Models: An Emerging Platform for Translational Cancer Research

Manuel Hidalgo

Manuel Hidalgo, Frederic Amant, Andrew V. Biankin, Eva Budinská, Annette T. Byrne, Carlos Caldas, Robert B. Clarke, Steven de Jong, Jos Jonkers, Gunhild Mari Mælandsmo, Sergio Roman-Roman, Joan Seoane, Livio Trusolino, and Alberto Villanueva for the EurOPDX Consortium

Abstract

Recently, there has been an increasing interest in the development and characterization of patient-derived tumor xenograft (PDX) models for cancer research. PDX models mostly retain the principal histologic and genetic characteristics of their donor tumor and remain stable across passages. These models have been shown to be predictive of clinical outcomes and are being used for preclinical drug evaluation, biomarker identification, biologic studies, and personalized medicine strategies. This article summarizes the current state of the art in this field, including methodologic issues, available collections, practical applications, challenges and shortcomings, and future directions, and introduces a European consortium of PDX models.

Significance: PDX models are increasingly used in translational cancer research. These models are useful for drug screening, biomarker development, and the preclinical evaluation of personalized medicine strategies. This review provides a timely overview of the key characteristics of PDX models and a detailed discussion of future directions in the field. *Cancer Discov; 4(9); 998–1013. ©2014 AACR.*

Cancer Discovery September 2014 4:998; Published OnlineFirst July 15, 2014; doi: 10.1158/2159-8290.CD-14-0001

Research Article

The Genetic Landscape of Clinical Resistance to RAF Inhibition in Metastatic Melanoma


Levi A. Garraway


Dirk Schadendorf

Eliezer M. Van Allen, Nikhil Wagle, Antje Sucker, Daniel J. Treacy, Cory M. Johannessen, Eva M. Goetz, Chelsea S. Place, Amaro Taylor-Weiner, Steven Whittaker, Gregory V. Kryukov, Eran Hodis, Mara Rosenberg, Aaron McKenna, Kristian Cibulskis, Deborah Farlow, Lisa Zimmer, Uwe Hillen, Ralf Gutzmer, Simone M. Goldinger, Selma Ugurel, Helen J. Gogas, Friederike Egberts, Carola Berking, Uwe Trefzer, Carmen Loquai, Benjamin Weide, Jessica C. Hassel, Stacey B. Gabriel, Scott L. Carter, Gad Getz, Levi A. Garraway, and Dirk Schadendorf on behalf of the Dermatologic Cooperative Oncology Group of Germany (DeCOG)

Abstract

Most patients with *BRAF*^{V600}-mutant metastatic melanoma develop resistance to selective RAF kinase inhibitors. The spectrum of clinical genetic resistance mechanisms to RAF inhibitors and options for salvage therapy are incompletely understood. We performed whole-exome sequencing on formalin-fixed, paraffin-embedded tumors from 45 patients with *BRAF*^{V600}-mutant metastatic melanoma who received vemurafenib or dabrafenib monotherapy. Genetic alterations in known or putative RAF inhibitor resistance genes were observed in 23 of 45 patients (51%). Besides previously characterized alterations, we discovered a "long tail" of new mitogen-activated protein kinase (MAPK) pathway alterations (*MAP2K2*, *MITF*) that confer RAF inhibitor resistance. In three cases, multiple resistance gene alterations were observed within the same tumor biopsy. Overall, RAF inhibitor therapy leads to diverse clinical genetic resistance mechanisms, mostly involving MAPK pathway reactivation. Novel therapeutic combinations may be needed to achieve durable clinical control of *BRAF*^{V600}-mutant melanoma. Integrating clinical genomics with preclinical screens may model subsequent resistance studies.

Significance: The use of RAF inhibitors for *BRAF*^{V600}-mutant metastatic melanoma improves patient outcomes, but most patients demonstrate early or acquired resistance to this targeted therapy. We reveal the genetic landscape of clinical resistance mechanisms to RAF inhibitors from patients using whole-exome sequencing, and experimentally assess new observed mechanisms to define potential subsequent treatment strategies. *Cancer Discov; 4(1); 94–109. ©2013 AACR.*

Cancer Discovery January 2014 4:94; Published OnlineFirst November 21, 2013; doi: 10.1158/2159-8290.CD-13-0617

Research Article

Acquired Resistance and Clonal Evolution in Melanoma during BRAF Inhibitor Therapy


Roger S. Lo

Hubing Shi, Willy Hugo, Xiangju Kong, Aayoung Hong, Richard C. Koya, Gatien Moriceau, Thinle Chodon, Rongqing Guo, Douglas B. Johnson, Kimberly B. Dahlman, Mark C. Kelley, Richard F. Kefford, Bartosz Chmielowski, John A. Glaspy, Jeffrey A. Sosman, Nicolas van Baren, Georgina V. Long, Antoni Ribas, and Roger S. Lo

Abstract

BRAF inhibitors elicit rapid antitumor responses in the majority of patients with *BRAF*^{V600}-mutant melanoma, but acquired drug resistance is almost universal. We sought to identify the core resistance pathways and the extent of tumor heterogeneity during disease progression. We show that mitogen-activated protein kinase reactivation mechanisms were detected among 70% of disease-progressive tissues, with *RAS* mutations, mutant *BRAF* amplification, and alternative splicing being most common. We also detected PI3K–PTEN–AKT–upregulating genetic alterations among 22% of progressive melanomas. Distinct molecular lesions in both core drug escape pathways were commonly detected concurrently in the same tumor or among multiple tumors from the same patient. Beyond harboring extensively heterogeneous resistance mechanisms, melanoma regrowth emerging from BRAF inhibitor selection displayed branched evolution marked by altered mutational spectra/signatures and increased fitness. Thus, melanoma genomic heterogeneity contributes significantly to BRAF inhibitor treatment failure, implying upfront, cotargeting of two core pathways as an essential strategy for durable responses.

Significance: This study provides critical insights into how human *BRAF*-mutant melanoma, a malignancy with marked mutational burden, escapes from BRAF inhibitors. Understanding the core resistance pathways as well as tumor heterogeneity, fitness, and mutational patterns, which emerge under drug selection, lays a foundation to rationalize clinical studies and investigate mechanisms of disease progression. *Cancer Discov; 4(1); 80–93. ©2013 AACR.*

Cancer Discovery January 2014 4:80; Published OnlineFirst November 21, 2013; doi: 10.1158/2159-8290.CD-13-0642

Research Article

The ALK Inhibitor Ceritinib Overcomes Crizotinib Resistance in Non–Small Cell Lung Cancer


Jennifer L. Harris


Alice T. Shaw


Jeffrey A. Engelman

Luc Friboulet, Nanxin Li, Ryohei Katayama, Christian C. Lee, Justin F. Gainor, Adam S. Crystal, Pierre-Yves Michellys, Mark M. Awad, Noriko Yanagitani, Sungjoon Kim, AnneMarie C. Pferdekamper, Jie Li, Shailaja Kasibhatla, Frank Sun, Xiuying Sun, Su Hua, Peter McNamara, Sidra Mahmood, Elizabeth L. Lockerman, Naoya Fujita, Makoto Nishio, Jennifer L. Harris, Alice T. Shaw, and Jeffrey A. Engelman

Abstract

Non–small cell lung cancers (NSCLC) harboring anaplastic lymphoma kinase (*ALK*) gene rearrangements invariably develop resistance to the ALK tyrosine kinase inhibitor (TKI) crizotinib. Herein, we report the first preclinical evaluation of the next-generation ALK TKI, ceritinib (LDK378), in the setting of crizotinib resistance. An interrogation of *in vitro* and *in vivo* models of acquired resistance to crizotinib, including cell lines established from biopsies of patients with crizotinib-resistant NSCLC, revealed that ceritinib potently overcomes crizotinib-resistant mutations. In particular, ceritinib effectively inhibits ALK harboring L1196M, G1269A, I1171T, and S1206Y mutations, and a cocrystal structure of ceritinib bound to ALK provides structural bases for this increased potency. However, we observed that ceritinib did not overcome two crizotinib-resistant ALK mutations, G1202R and F1174C, and one of these mutations was identified in 5 of 11 biopsies from patients with acquired resistance to ceritinib. Altogether, our results demonstrate that ceritinib can overcome crizotinib resistance, consistent with clinical data showing marked efficacy of ceritinib in patients with crizotinib-resistant disease.

Significance: The second-generation ALK inhibitor ceritinib can overcome several crizotinib-resistant mutations and is potent against several *in vitro* and *in vivo* laboratory models of acquired resistance to crizotinib. These findings provide the molecular basis for the marked clinical activity of ceritinib in patients with *ALK*-positive NSCLC with crizotinib-resistant disease. *Cancer Discov; 4(6); 662–73. ©2014 AACR.*

Cancer Discovery June 2014 4:662; Published OnlineFirst March 27, 2014; doi: 10.1158/2159-8290.CD-13-0846

Research Article

AZD9291, an Irreversible EGFR TKI, Overcomes T790M-Mediated Resistance to EGFR Inhibitors in Lung Cancer


Darren A.E. Cross


William Pao

Darren A.E. Cross, Susan E. Ashton, Serban Ghiorghiu, Cath Eberlein, Caroline A. Nebhan, Paula J. Spitzler, Jonathon P. Orme, M. Raymond V. Finlay, Richard A. Ward, Martine J. Mellor, Gareth Hughes, Amar Rahi, Vivien N. Jacobs, Monica Red Brewer, Eiki Ichihara, Jing Sun, Hailing Jin, Peter Ballard, Katherine Al-Kadhimi, Rachel Rowlinson, Teresa Klinowska, Graham H.P. Richmond, Mireille Cantarini, Dong-Wan Kim, Malcolm R. Ranson, and William Pao

Abstract

First-generation EGFR tyrosine kinase inhibitors (EGFR TKI) provide significant clinical benefit in patients with advanced *EGFR*-mutant (EGFRm$^+$) non–small cell lung cancer (NSCLC). Patients ultimately develop disease progression, often driven by acquisition of a second T790M EGFR TKI resistance mutation. AZD9291 is a novel oral, potent, and selective third-generation irreversible inhibitor of both EGFRm$^+$ sensitizing and T790M resistance mutants that spares wild-type EGFR. This mono-anilino–pyrimidine compound is structurally distinct from other third-generation EGFR TKIs and offers a pharmacologically differentiated profile from earlier generation EGFR TKIs. Preclinically, the drug potently inhibits signaling pathways and cellular growth in both EGFRm$^+$ and EGFRm$^+$/T790M$^+$ mutant cell lines *in vitro*, with lower activity against wild-type EGFR lines, translating into profound and sustained tumor regression in *EGFR*-mutant tumor xenograft and transgenic models. The treatment of 2 patients with advanced EGFRm$^+$ T790M$^+$ NSCLC is described as proof of principle.

Significance: We report the development of a novel structurally distinct third-generation EGFR TKI, AZD9291, that irreversibly and selectively targets both sensitizing and resistant T790M$^+$ mutant EGFR while harboring less activity toward wild-type EGFR. AZD9291 is showing promising responses in a phase I trial even at the first-dose level, with first published clinical proof-of-principle validation being presented. *Cancer Discov; 4(9); 1046–61. ©2014 AACR.*

Cancer Discovery September 2014 4:1046; Published OnlineFirst June 3, 2014; doi: 10.1158/2159-8290.CD-14-0337

Cancer Epidemiology, Biomarkers & Prevention

Timothy R. Rebbeck, PhD
Editor-in-Chief

Scope

Cancer Epidemiology, Biomarkers & Prevention publishes original, peer-reviewed, population-based research on cancer etiology, prevention, surveillance, and survivorship. The following topics are of special interest: descriptive, analytical, and molecular epidemiology; biomarkers including assay development, validation, and application; chemoprevention and other types of prevention research in the context of descriptive and observational studies; the role of behavioral factors in cancer etiology and prevention; survivorship studies; risk factors; and the science of cancer health disparities. Besides welcoming manuscripts that address individual subjects in any of the relevant disciplines, *Cancer Epidemiology, Biomarkers & Prevention* editors encourage the submission of manuscripts with a transdisciplinary approach.

Review Article

Prognostic Role of Platelet to Lymphocyte Ratio in Solid Tumors: A Systematic Review and Meta-Analysis

Arnoud J. Templeton, Olga Ace, Mairéad G. McNamara, Mustafa Al-Mubarak, Francisco E. Vera-Badillo, Thomas Hermanns, Boštjan Šeruga, Alberto Ocaña, Ian F. Tannock, and Eitan Amir

Eitan Amir

Abstract

Background: Inflammation influences cancer development and progression. An elevated platelet to lymphocyte ratio (PLR), a marker of inflammation, has been linked to poor prognosis in several malignancies. Here, we quantify the prognostic impact of this biomarker.

Methods: A systematic review of databases was conducted to identify publications exploring the association of blood PLR and overall survival (OS) in solid tumors. Data were pooled in a meta-analysis. Pooled HRs for OS by disease group and by PLR cutoff groups were computed and weighted using generic inverse-variance and random-effect modeling.

Results: Twenty studies comprising 12,754 patients were assessed. Cutoffs for PLR defining risk groups ranged from 150 to 300 and were dichotomous (12 studies; group 1) or split into three groups (<150/150–300/>300, 8 studies; group 2). Higher PLR was associated with significantly worse OS in group 1 [HR = 1.87; 95% confidence interval (CI, 1.49–2.34); $P < 0.001$] and with a nonsignificant association in group 2 (HR per higher category = 1.21; 95% CI, 0.97–1.50; $P = 0.10$). The size of effect of PLR on OS was greater for metastatic disease ($HR_{[group\ 1]} = 2.0$; 95% CI, 1.6–2.7; $HR_{[group\ 2]} = 1.6$; 95% CI, 1.1–2.4) than for early-stage disease ($HR_{[group\ 1]} = 1.5$; 95% CI, 1.0–2.2; $HR_{[group\ 2]} = 1.0$; 95% CI, 0.8–1.3). A significant association was observed for colorectal, hepatocellular, gastroesophageal, ovarian, and pancreatic carcinoma in group 1 and for colorectal cancers in group 2.

Conclusion: A high PLR is associated with worse OS in various solid tumors. Further research of its regulation and relevance in daily practice is warranted.

Impact: PLR is a readily available and inexpensive biomarker with independent prognostic value in solid tumors. *Cancer Epidemiol Biomarkers Prev; 23(7); 1204–12. ©2014 AACR.*

Cancer Epidemiol Biomarkers Prev July 2014 23:1204; Published OnlineFirst May 3, 2014; doi: 10.1158/1055-9965.EPI-14-0146

Research Article

Cancer in Africa 2012

D. Maxwell Parkin, Freddie Bray, Jacques Ferlay, and Ahmedin Jemal

Ahmedin Jemal

Abstract

Background: Noncommunicable diseases, and especially cancers, are recognized as an increasing problem for low and middle income countries. Effective control programs require adequate information on the size, nature, and evolution of the health problem that they pose.

Methods: We present estimates of the incidence and mortality of cancer in Africa in 2012, derived from "GLOBOCAN 2012," published by the International Agency for Research on Cancer.

Results: There were 847,000 new cancer cases (6% of the world total) and 591,000 deaths (7.2% of the world total) in the 54 countries of Africa in 2012, with about three quarters in the 47 countries of Sub-Saharan Africa. While the cancer profiles often differ markedly between regions, the most common cancers in men were prostate (16.4% of new cancers), liver (10.7%), and Kaposi sarcoma (6.7%); in women, by far the most important are cancers of the breast (27.6% of all cancers) and cervix uteri (20.4%).

Conclusions: There are still deficiencies in surveillance systems, particularly in Sub-Saharan Africa and, specifically, of their most vital component, population-based cancer registries. With the number of annual cancer cases and deaths likely to increase by at least 70% by 2030, there is a pressing need for a coordinated approach to improving the extent and quality of services for cancer control in Africa, and better surveillance systems with which they can be planned and monitored.

Impact: The results are the best data currently available and provide a reasonable appraisal of the cancer situation in Africa. *Cancer Epidemiol Biomarkers Prev; 23(6); 953–66. ©2014 AACR.*

Cancer Epidemiol Biomarkers Prev June 2014 23:953; Published OnlineFirst April 3, 2014; doi: 10.1158/1055-9965.EPI-14-0281

Research Article

Chronic Inflammation in Benign Prostate Tissue Is Associated with High-Grade Prostate Cancer in the Placebo Arm of the Prostate Cancer Prevention Trial

Angelo M. De Marzo

Elizabeth A. Platz

Bora Gurel, M. Scott Lucia, Ian M. Thompson Jr, Phyllis J. Goodman, Catherine M. Tangen, Alan R. Kristal, Howard L. Parnes, Ashraful Hoque, Scott M. Lippman, Siobhan Sutcliffe, Sarah B. Peskoe, Charles G. Drake, William G. Nelson, Angelo M. De Marzo, and Elizabeth A. Platz

Abstract

Background: Chronic inflammation is hypothesized to influence prostate cancer development, although a definitive link has not been established.

Methods: Prostate cancer cases (N = 191) detected on a for-cause (clinically indicated) or end-of-study (protocol directed) biopsy, and frequency-matched controls (N = 209), defined as negative for cancer on an end-of-study biopsy, were sampled from the placebo arm of the Prostate Cancer Prevention Trial. Inflammation prevalence and extent in benign areas of biopsy cores were visually assessed using digital images of hematoxylin and eosin–stained sections. Logistic regression was used to estimate associations.

Results: Of note, 86.2% of cases and 78.2% of controls had at least one biopsy core (of three assessed) with inflammation in benign areas, most of which was chronic. Men who had at least one biopsy core with inflammation had 1.78 [95% confidence interval (CI), 1.04–3.06] times the odds of prostate cancer compared with men who had zero cores with inflammation. The association was stronger for high-grade disease (Gleason sum 7–10, N = 94; OR, 2.24; 95% CI, 1.06–4.71). These patterns were present when restricting to cases and controls in whom intraprostatic inflammation was the least likely to have influenced biopsy recommendation because their prostate-specific antigen (PSA) was low (<2 ng/mL at biopsy).

Conclusion: Inflammation, most of which was chronic, was common in benign prostate tissue, and was positively associated with prostate cancer, especially high grade. The association did not seem to be due to detection bias.

Impact: This study supports an etiologic link between inflammation and prostate carcinogenesis, and suggests an avenue for prevention by mitigating intraprostatic inflammation. *Cancer Epidemiol Biomarkers Prev; 23(5); 847–56. ©2014 AACR.*

Cancer Epidemiol Biomarkers Prev May 2014 23:847; Published OnlineFirst April 18, 2014; doi: 10.1158/1055-9965.EPI-13-1126

Research Article

Programmed Cell Death 1 (PD-1) and Its Ligand (PD-L1) in Common Cancers and Their Correlation with Molecular Cancer Type


Zoran Gatalica

Zoran Gatalica, Carrie Snyder, Todd Maney, Anatole Ghazalpour, Daniel A. Holterman, Nianqing Xiao, Peggy Overberg, Inga Rose, Gargi D. Basu, Semir Vranic, Henry T. Lynch, Daniel D. Von Hoff, and Omid Hamid

Abstract

Cancer cells expressing PD-1 ligands (PD-L1/PD-L2) inhibit immune-modulatory T-cell activation facilitating disease progression. Preliminary clinical trials exploring interruption of PD-1/PD-L1 signaling showed benefit in several cancer types. We analyzed the distribution of PD-1–positive tumor-infiltrating lymphocytes (TIL) and cancer cells' expression of PD-L1 in a molecularly profiled cohort of 437 malignancies (380 carcinomas, 33 sarcomas, and 24 melanomas). We showed that the presence of PD-1$^+$ TILs significantly varied among cancer types (from 0% in extraskeletal myxoid chondrosarcomas to 93% in ovarian cancer), and was generally associated with the increased number of mutations in tumor cells ($P = 0.029$). Cancer cell expression of PD-L1 varied from absent (in Merkel cell carcinomas) to 100% (in chondro- and liposarcomas), but showed the inverse association with the number of detected mutations ($P = 0.004$). Both PD-1 and PD-L1 expression were significantly higher in triple-negative breast cancers (TNBC) than in non-TNBC ($P < 0.001$ and 0.017, respectively). Similarly, MSI-H colon cancers had higher PD-1 and PD-L1 expression than the microsatellite stable tumors ($P = 0.002$ and 0.02, respectively). *TP53*-mutated breast cancers had significantly higher PD-1 positivity than those harboring other driver mutations (e.g., *PIK3CA*; $P = 0.002$). In non–small cell lung cancer, PD-1/PD-L1 coexpression was identified in 8 cases (19%), which lacked any other targetable alterations (e.g., *EGFR*, *ALK*, or *ROS1*). Our study demonstrated the utility of exploring the expression of two potentially targetable immune checkpoint proteins (PD-1/PD-L1) in a substantial proportion of solid tumors, including some aggressive subtypes that lack other targeted treatment modalities. *Cancer Epidemiol Biomarkers Prev; 23(12); 2965–70. ©2014 AACR.*

Cancer Epidemiol Biomarkers Prev December 2014 23:2965; Published OnlineFirst November 12, 2014; doi: 10.1158/1055-9965. EPI-14-0654

Research Article

Dietary Inflammatory Index and Risk of Colorectal Cancer in the Iowa Women's Health Study


James R. Hébert

Nitin Shivappa, Anna E. Prizment, Cindy K. Blair, David R. Jacobs Jr, Susan E. Steck, and James R. Hébert

Abstract

Background: Colorectal cancer, the third most common cancer in the United States, has a natural history that usually encompasses several decades. Dietary components have been implicated in the etiology of colorectal cancer, perhaps through their effect on inflammation.

Methods: We examined the ability of the dietary inflammatory index (DII) to predict colorectal cancer in the Iowa Women's Health Study. The DII was computed based on dietary intake assessed by a 121-item food frequency questionnaire in this cohort of 34,703 women, ages 55 to 69 years, free of any self-reported prior malignancy at enrollment in 1986. Incident colorectal cancer cases were identified through linkage with the State Health Registry of Iowa (a Surveillance, Epidemiology, and End Results program member). Cox proportional hazards regression was used to estimate HRs. Through the end of 2010, 1,636 incident colorectal cancers were identified, including 1,329 colon and 325 rectal cancers.

Results: Multivariable analysis, adjusting for body mass index, smoking status, pack-years of smoking, hormone replacement therapy, education, diabetes, and total energy intake, revealed positive associations between higher DII and colorectal cancer risk [HR for $DII_{continuous}$: 1.07 per unit increase in DII (corresponding to 0.5 SD unit increase); 95% confidence interval (CI), 1.01–1.13; HR for $DII_{quintiles}$: Q5 vs. Q1 = 1.20; 95% CI, 1.01–1.43]. HRs for DII were similar for colon cancer and rectal cancer, though not statistically significant for rectal cancer.

Conclusions: These results indicate that a proinflammatory diet, as indicated by higher DII scores, was associated with higher risk of developing colorectal cancer.

Impact: Proinflammatory diets are associated with increased risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev; 23(11); 2383–92. ©2014 AACR.*

Cancer Epidemiol Biomarkers Prev November 2014 23:2383; Published OnlineFirst August 25, 2013; doi: 10.1158/1055-9965. EPI-14-0537

Cancer Immunology Research

Glenn Dranoff, MD
Founding Editor-in-Chief

Scope

Cancer Immunology Research publishes outstanding original articles reporting major advances in cancer immunology that span the discipline from basic investigations in host-tumor interactions to developmental therapeutics in model systems, early translational studies in patients, and late-stage clinical trials. The Journal disseminates knowledge of immunology to the cancer research community, catalyzing cross-disciplinary work that yields a deeper understanding of the host-tumor relationship, more potent cancer treatments, and improved clinical outcomes.

Review Article

Combining Radiation and Immunotherapy: A New Systemic Therapy for Solid Tumors?

James W. Welsh

Chad Tang, Xiaohong Wang, Hendrick Soh, Steven Seyedin, Maria Angelica Cortez, Sunil Krishnan, Erminia Massarelli, David Hong, Aung Naing, Adi Diab, Daniel Gomez, Huiping Ye, John Heymach, Ristuko Komaki, James P. Allison, Padmanee Sharma, and James W. Welsh

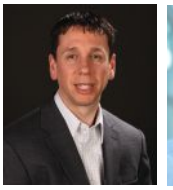
Abstract

With the recent success of checkpoint inhibitors and other immunomodulating agents, there has been renewed interest in the combination of such agents with radiation. The biologic premise behind such a strategy is that the tumor-antigen release achieved by localized radiation will promote specific tumor targeting by the adaptive immune system, which can be augmented further by systemic immune-stimulating agents. In this manner, clinicians hope to induce a phenomenon known as the abscopal effect, whereby localized radiation results in immune-mediated tumor regression in disease sites well outside of the radiation field. Herein, we present a comprehensive overview of the early clinical and preclinical evidence behind this approach. *Cancer Immunol Res; 2(9); 831–8. ©2014 AACR.*

Cancer Immunol Res September 2014 2:831; doi: 10.1158/2326-6066.CIR-14-0069

Research Article

Mesothelin-Specific Chimeric Antigen Receptor mRNA-Engineered T Cells Induce Antitumor Activity in Solid Malignancies


Gregory L. Beatty


Carl H. June

Gregory L. Beatty, Andrew R. Haas, Marcela V. Maus, Drew A. Torigian, Michael C. Soulen, Gabriela Plesa, Anne Chew, Yangbing Zhao, Bruce L. Levine, Steven M. Albelda, Michael Kalos, and Carl H. June

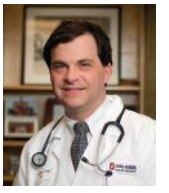
Abstract

Off-target toxicity due to the expression of target antigens in normal tissue represents a major obstacle to the use of chimeric antigen receptor (CAR)-engineered T cells for treatment of solid malignancies. To circumvent this issue, we established a clinical platform for engineering T cells with transient CAR expression by using *in vitro* transcribed mRNA encoding a CAR that includes both the CD3-ζ and 4-1BB costimulatory domains. We present two case reports from ongoing trials indicating that adoptive transfer of mRNA CAR T cells that target mesothelin (CARTmeso cells) is feasible and safe without overt evidence of off-tumor on-target toxicity against normal tissues. CARTmeso cells persisted transiently within the peripheral blood after intravenous administration and migrated to primary and metastatic tumor sites. Clinical and laboratory evidence of antitumor activity was shown in both patients, and the CARTmeso cells elicited an antitumor immune response revealed by the development of novel antiself antibodies. These data show the potential of using mRNA-engineered T cells to evaluate, in a controlled manner, potential off-tumor on-target toxicities and show that short-lived CAR T cells can induce epitope spreading and mediate antitumor activity in patients with advanced cancer. Thus, these findings support the development of mRNA CAR-based strategies for carcinoma and other solid tumors. *Cancer Immunol Res; 2(2); 112–20. ©2013 AACR.*

Cancer Immunol Res February 2014 2:112; Published OnlineFirst December 19, 2013; doi: 10.1158/2326-6066.CIR-13-0170

Research Article

Bevacizumab plus Ipilimumab in Patients with Metastatic Melanoma


F. Stephen Hodi

F. Stephen Hodi, Donald Lawrence, Cecilia Lezcano, Xinqi Wu, Jun Zhou, Tetsuro Sasada, Wanyong Zeng, Anita Giobbie-Hurder, Michael B. Atkins, Nageatte Ibrahim, Philip Friedlander, Keith T. Flaherty, George F. Murphy, Scott Rodig, Elsa F. Velazquez, Martin C. Mihm Jr, Sara Russell, Pamela J. DiPiro, Jeffrey T. Yap, Nikhil Ramaiya, Annick D. Van den Abbeele, Maria Gargano, and David McDermott

Abstract

Ipilimumab improves survival in advanced melanoma and can induce immune-mediated tumor vasculopathy. Besides promoting angiogenesis, vascular endothelial growth factor (VEGF) suppresses dendritic cell maturation and modulates lymphocyte endothelial trafficking. This study investigated the combination of CTLA4 blockade with ipilimumab and VEGF inhibition with bevacizumab. Patients with metastatic melanoma were treated in four dosing cohorts of ipilimumab (3 or 10 mg/kg) with four doses at 3-week intervals and then every 12 weeks, and bevacizumab (7.5 or 15 mg/kg) every 3 weeks. Forty-six patients were treated. Inflammatory events included giant cell arteritis ($n = 1$), hepatitis ($n = 2$), and uveitis ($n = 2$). On-treatment tumor biopsies revealed activated vessel endothelium with extensive $CD8^+$ and macrophage cell infiltration. Peripheral blood analyses demonstrated increases in $CCR7^{+/-}/CD45RO^+$ cells and anti-galectin antibodies. Best overall response included 8 partial responses, 22 instances of stable disease, and a disease-control rate of 67.4%. Median survival was 25.1 months. Bevacizumab influences changes in tumor vasculature and immune responses with ipilimumab administration. The combination of bevacizumab and ipilimumab can be safely administered and reveals VEGF-A blockade influences on inflammation, lymphocyte trafficking, and immune regulation. These findings provide a basis for further investigating the dual roles of angiogenic factors in blood vessel formation and immune regulation, as well as future combinations of antiangiogenesis agents and immune checkpoint blockade. *Cancer Immunol Res; 2(7); 632–42. ©2014 AACR.*

Cancer Immunol Res July 2014 2:632; Published OnlineFirst April 21, 2014; doi: 10.1158/2326-6066.CIR-14-0053

Research Article

Immunotherapy Converts Nonimmunogenic Pancreatic Tumors into Immunogenic Foci of Immune Regulation

Eric R. Lutz, Annie A. Wu, Elaine Bigelow, Rajni Sharma, Guanglan Mo, Kevin Soares, Sara Solt, Alvin Dorman, Anthony Wamwea, Allison Yager, Daniel Laheru, Christopher L. Wolfgang, Jiang Wang, Ralph H. Hruban, Robert A. Anders, Elizabeth M. Jaffee, and Lei Zheng


Lei Zheng


Elizabeth M. Jaffee

Abstract

Pancreatic ductal adenocarcinoma (PDAC) is considered a "nonimmunogenic" neoplasm. Single-agent immunotherapies have failed to demonstrate significant clinical activity in PDAC and other "nonimmunogenic" tumors, in part due to a complex tumor microenvironment (TME) that provides a formidable barrier to immune infiltration and function. We designed a neoadjuvant and adjuvant clinical trial comparing an irradiated, granulocyte-macrophage colony-stimulating factor (GM-CSF)–secreting, allogeneic PDAC vaccine (GVAX) given as a single agent or in combination with low-dose cyclophosphamide to deplete regulatory T cells (Treg) as a means to study how the TME is altered by immunotherapy. Examination of resected PDACs revealed the formation of vaccine-induced intratumoral tertiary lymphoid aggregates in 33 of 39 patients 2 weeks after vaccine treatment. Immunohistochemical analysis showed these aggregates to be regulatory structures of adaptive immunity. Microarray analysis of microdissected aggregates identified gene-expression signatures in five signaling pathways involved in regulating immune-cell activation and trafficking that were associated with improved postvaccination responses. A suppressed Treg pathway and an enhanced Th17 pathway within these aggregates were associated with improved survival, enhanced postvaccination mesothelin-specific T-cell responses, and increased intratumoral Teff:Treg ratios. This study provides the first example of immune-based therapy converting a "nonimmunogenic" neoplasm into an "immunogenic" neoplasm by inducing infiltration of T cells and development of tertiary lymphoid structures in the TME. Post-GVAX T-cell infiltration and aggregate formation resulted in the upregulation of immunosuppressive regulatory mechanisms, including the PD-1–PD-L1 pathway, suggesting that patients with vaccine-primed PDAC may be better candidates than vaccine-naïve patients for immune checkpoint and other immunomodulatory therapies. *Cancer Immunol Res; 2(7); 616–31. ©2014 AACR.*

Cancer Immunol Res July 2014 2:616; Published OnlineFirst June 18, 2014; doi: 10.1158/2326-6066.CIR-14-0027

Research Article

Response to BRAF Inhibition in Melanoma Is Enhanced When Combined with Immune Checkpoint Blockade

Zachary A. Cooper, Vikram R. Juneja, Peter T. Sage, Dennie T. Frederick, Adriano Piris, Devarati Mitra, Jennifer A. Lo, F. Stephen Hodi, Gordon J. Freeman, Marcus W. Bosenberg, Martin McMahon, Keith T. Flaherty, David E. Fisher, Arlene H. Sharpe, and Jennifer A. Wargo


Jennifer A. Wargo

Abstract

BRAF-targeted therapy results in objective responses in the majority of patients; however, the responses are short lived (~6 months). In contrast, treatment with immune checkpoint inhibitors results in a lower response rate, but the responses tend to be more durable. BRAF inhibition results in a more favorable tumor microenvironment in patients, with an increase in $CD8^+$ T-cell infiltrate and a decrease in immunosuppressive cytokines. There is also increased expression of the immunomodulatory molecule PDL1, which may contribute to the resistance. On the basis of these findings, we hypothesized that BRAF-targeted therapy may synergize with the PD1 pathway blockade to enhance antitumor immunity. To test this hypothesis, we developed a BRAF(V600E)/$Pten^{-/-}$ syngeneic tumor graft immunocompetent mouse model in which BRAF inhibition leads to a significant increase in the intratumoral $CD8^+$ T-cell density and cytokine production, similar to the effects of BRAF inhibition in patients. In this model, $CD8^+$ T cells were found to play a critical role in the therapeutic effect of BRAF inhibition. Administration of anti-PD1 or anti-PDL1 together with a BRAF inhibitor led to an enhanced response, significantly prolonging survival and slowing tumor growth, as well as significantly increasing the number and activity of tumor-infiltrating lymphocytes. These results demonstrate synergy between combined BRAF-targeted therapy and immune checkpoint blockade. Although clinical trials combining these two strategies are ongoing, important questions still remain unanswered. Further studies using this new melanoma mouse model may provide therapeutic insights, including optimal timing and sequence of therapy. *Cancer Immunol Res; 2(7); 643–54. ©2014 AACR.*

Cancer Immunol Res July 2014 2:643; Published OnlineFirst April 29, 2014; doi: 10.1158/2326-6066.CIR-13-0215

Cancer Prevention Research

Scott M. Lippman, MD
Editor-in-Chief

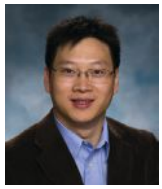
Scope

Cancer Prevention Research is devoted exclusively to cancer prevention. The Journal publishes important original studies, reviews, and perspectives within the major topic areas of biology of premalignancy, risk factors and risk assessment, early detection research, immunoprevention, and chemopreventive and other interventions, including the basic science behind them. *Cancer Prevention Research* comprises preclinical, clinical, and translational research, with special attention given to molecular discoveries and an emphasis on building a translational bridge between the basic and clinical sciences.

Review Article

Repurposing of Metformin and Aspirin by Targeting AMPK-mTOR and Inflammation for Pancreatic Cancer Prevention and Treatment

Wen Yue, Chung S. Yang, Robert S. DiPaola, and Xiang-Lin Tan



Xiang-Lin Tan

Abstract

Pancreatic cancer, as the fourth leading cause of cancer-related deaths, carries a poor prognosis with a median survival of 6 months and a dismal 5-year survival rate of 3% to 5%. These statistics highlight an urgent need for novel chemopreventive and therapeutic strategies for this malignancy. Metformin and aspirin have been explored as two emerging cancer chemoprevention agents for different types of cancers, including pancreatic cancer. Here, we review the effects of both metformin and aspirin on pancreatic tumorigenesis and their potential actions in pancreatic cancer. Special attention is paid to their effects on the important signaling pathways of pancreatic cancer development as well as possible mechanisms for synergy between these two agents. For metformin, the most important mechanism may involve the inhibition of mTOR signaling via AMP-activated protein kinase (AMPK)-dependent and -independent pathways. For aspirin, the major mechanism is the anti-inflammatory action through the inhibition of COX-1/COX-2 and modulation of the NFκB or STAT3 pathway. In addition, aspirin may activate AMPK, and both agents may affect Notch, Wnt/β-catenin, and other signaling pathways. The combination of metformin and aspirin will provide additive and possibly synergistic effects for the prevention and treatment of pancreatic cancer. *Cancer Prev Res; 7(4); 388–97. ©2014 AACR.*

Cancer Prev Res April 2014 7:388; Published OnlineFirst February 11, 2014; doi: 10.1158/1940-6207.CAPR-13-0337

Research Article

Nutrition and Physical Activity Cancer Prevention Guidelines, Cancer Risk, and Mortality in the Women's Health Initiative


Cynthia A. Thomson

Cynthia A. Thomson, Marjorie L. McCullough, Betsy C. Wertheim, Rowan T. Chlebowski, Maria Elena Martinez, Marcia L. Stefanick, Thomas E. Rohan, JoAnn E. Manson, Hilary A. Tindle, Judith Ockene, Mara Z. Vitolins, Jean Wactawski-Wende, Gloria E. Sarto, Dorothy S. Lane, and Marian L. Neuhouser

Abstract

Healthy lifestyle behaviors are recommended to reduce cancer risk and overall mortality. Adherence to cancer-preventive health behaviors and subsequent cancer risk has not been evaluated in a diverse sample of postmenopausal women. We examined the association between the American Cancer Society (ACS) Nutrition and Physical Activity Cancer Prevention Guidelines score and risk of incident cancer, cancer-specific mortality, and all-cause mortality in 65,838 postmenopausal women enrolled in the Women's Health Initiative Observational Study. ACS guidelines scores (0–8 points) were determined from a combined measure of diet, physical activity, body mass index (current and at age 18 years), and alcohol consumption. After a mean follow-up of 12.6 years, 8,632 incident cancers and 2,356 cancer deaths were identified. The highest ACS guidelines scores compared with the lowest were associated with a 17% lower risk of any cancer [HR, 0.83; 95% confidence interval (CI), 0.75–0.92], 22% lower risk of breast cancer (HR, 0.78; 95% CI, 0.67–0.92), 52% lower risk of colorectal cancer (HR, 0.48; 95% CI, 0.32–0.73), 27% lower risk of all-cause mortality, and 20% lower risk of cancer-specific mortality (HR, 0.80; 95% CI, 0.71–0.90). Associations with lower cancer incidence and mortality were generally strongest among Asian, black, and Hispanic women and weakest among non-Hispanic whites. Behaviors concordant with Nutrition and Physical Activity Cancer Prevention Guidelines were associated with lower risk of total, breast, and colorectal cancers and lower cancer-specific mortality in postmenopausal women. *Cancer Prev Res; 7(1); 42–53. ©2014 AACR.*

Cancer Prev Res January 2014 7:42; doi: 10.1158/1940-6207.CAPR-13-0258

Research Article

Metformin and Cancer Risk and Mortality: A Systematic Review and Meta-analysis Taking into Account Biases and Confounders


Eva Szabo


Andrea DeCensi

Sara Gandini, Matteo Puntoni, Brandy M. Heckman-Stoddard, Barbara K. Dunn, Leslie Ford, Andrea DeCensi, and Eva Szabo

Abstract

Previous meta-analyses have shown that the antidiabetic agent metformin is associated with reduced cancer incidence and mortality. However, this effect has not been consistently demonstrated in animal models and recent epidemiologic studies. We performed a meta-analysis with a focus on confounders and biases, including body mass index (BMI), study type, and time-related biases. We identified 71 articles published between January 1, 1966, and May 31, 2013, through Pubmed, ISI Web of Science (Science Citation Index Expanded), Embase, and the Cochrane library that were related to metformin and cancer incidence or mortality. Study characteristics and outcomes were abstracted for each study that met inclusion criteria. We included estimates from 47 independent studies and 65,540 cancer cases in patients with diabetes. Overall cancer incidence was reduced by 31% [summary relative risk (SRR), 0.69; 95% confidence interval (CI), 0.52–0.90], although between-study heterogeneity was considerable (I^2 = 88%). Cancer mortality was reduced by 34% (SRR, 0.66; 95% CI, 0.54–0.81; I^2 = 21%). BMI-adjusted studies and studies without time-related biases also showed significant reduction in cancer incidence (SRR, 0.82; 95% CI, 0.70–0.96 with I^2 = 76% and SRR, 0.90; 95% CI, 0.89–0.91 with I^2 = 56%, respectively), albeit with lesser magnitude (18% and 10% reduction, respectively). However, studies of cancer mortality and individual organ sites did not consistently show significant reductions across all types of analyses. Although these associations may not be causal, our results show that metformin may reduce cancer incidence and mortality in patients with diabetes. However, the reduction seems to be of modest magnitude and not affecting all populations equally. Clinical trials are needed to determine if these observations apply to nondiabetic populations and to specific organ sites. *Cancer Prev Res; 7(9); 867–85. ©2014 AACR.*

Cancer Prev Res September 2014 7:867; Published OnlineFirst July 1, 2014; doi: 10.1158/1940-6207.CAPR-13-0424

Research Article

Temporal and Spatial Evolution of Somatic Chromosomal Alterations: A Case-Cohort Study of Barrett's Esophagus

Brian J. Reid

Xiaohong Li, Patricia C. Galipeau, Thomas G. Paulson, Carissa A. Sanchez, Jessica Arnaudo, Karen Liu, Cassandra L. Sather, Rumen L. Kostadinov, Robert D. Odze, Mary K. Kuhner, Carlo C. Maley, Steven G. Self, Thomas L. Vaughan, Patricia L. Blount, and Brian J. Reid

Abstract

All cancers are believed to arise by dynamic, stochastic somatic genomic evolution with genome instability, generation of diversity, and selection of genomic alterations that underlie multistage progression to cancer. Advanced esophageal adenocarcinomas have high levels of somatic copy number alterations. Barrett's esophagus is a risk factor for developing esophageal adenocarcinoma, and somatic chromosomal alterations (SCA) are known to occur in Barrett's esophagus. The vast majority (~95%) of individuals with Barrett's esophagus do not progress to esophageal adenocarcinoma during their lifetimes, but a small subset develop esophageal adenocarcinoma, many of which arise rapidly even in carefully monitored patients without visible endoscopic abnormalities at the index endoscopy. Using a well-designed, longitudinal case-cohort study, we characterized SCA as assessed by single-nucleotide polymorphism arrays over space and time in 79 "progressors" with Barrett's esophagus as they approach the diagnosis of cancer and 169 "nonprogressors" with Barrett's esophagus who did not progress to esophageal adenocarcinoma over more than 20,425 person-months of follow-up. The genomes of nonprogressors typically had small localized deletions involving fragile sites and 9p loss/copy neutral LOH that generate little genetic diversity and remained relatively stable over prolonged follow-up. As progressors approach the diagnosis of cancer, their genomes developed chromosome instability with initial gains and losses, genomic diversity, and selection of SCAs followed by catastrophic genome doublings. Our results support a model of differential disease dynamics in which nonprogressor genomes largely remain stable over prolonged periods, whereas progressor genomes evolve significantly increased SCA and diversity within four years of esophageal adenocarcinoma diagnosis, suggesting a window of opportunity for early detection. *Cancer Prev Res; 7(1); 114–27. ©2013 AACR.*

Cancer Prev Res January 2014 7:114; Published OnlineFirst November 19, 2013; doi: 10.1158/1940-6207.CAPR-13-0289

Research Article

Requirement and Epigenetics Reprogramming of Nrf2 in Suppression of Tumor Promoter TPA-Induced Mouse Skin Cell Transformation by Sulforaphane

Ah-Ng Tony Kong

Zheng-Yuan Su, Chengyue Zhang, Jong Hun Lee, Limin Shu, Tien-Yuan Wu, Tin Oo Khor, Allan H. Conney, Yao-Ping Lu, and Ah-Ng Tony Kong

Abstract

Nrf2 is a transcription factor that plays critical roles in regulating the expression of cellular defensive antioxidants and detoxification enzymes. However, the role of Nrf2 and Nrf2's epigenetics reprogramming in skin tumor transformation is unknown. In this study, we investigated the inhibitory role and epigenetics of Nrf2 on tumor transformation induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in mouse skin epidermal JB6 (JB6 P+) cells and the anticancer effect of sulforaphane (SFN), an isothiocyanate found in cruciferous vegetables. After five days of treatment, SFN significantly inhibited TPA-induced JB6 cellular transformation and SFN enhanced the nuclear translocation of Nrf2 and increased the mRNA and protein levels of the Nrf2 target genes HO-1, NQO1 and UGT1A1. Knockdown of Nrf2 attenuated the induction of Nrf2, HO-1 and NQO1 by SFN, enhanced TPA-induced colony formation and dampened the inhibitory effect of SFN on TPA-induced JB6 transformation. Epigenetics investigation using bisulfite genomic sequencing showed that SFN decreased the methylation ratio of the first 15 CpGs of the Nrf2 gene promoter, which was corroborated by increased Nrf2 mRNA expression. Furthermore, SFN strongly reduced the protein expression of DNA methyltransferases (DNMT1, DNMT3a and DNMT3b). SFN also inhibited the total histone deacetylase (HDAC) activity and decreased the protein expression of HDAC1, HDAC2, HDAC3 and HDAC4. Collectively, these results suggest that the anti-cancer effect of SFN against TPA-induced neoplastic transformation of mouse skin could involve the epigenetic reprogramming of anti-cancer genes such as Nrf2, leading to the epigenetic reactivation of Nrf2 and the subsequent induction of downstream target genes involved in cellular protection. *Cancer Prev Res; 7(3); 319–29. ©2014 AACR.*

Cancer Prev Res March 2014 7:319; Published January 17, 2014; doi: 10.1158/1940-6207.CAPR-13-0313-T

Cancer Research

George C. Prendergast, PhD
Editor-in-Chief

Scope

Cancer Research is the most frequently cited cancer journal in the world. The Journal publishes original studies, reviews, and opinion pieces offering significance and broad impact to a diverse audience spanning basic, preclinical, clinical, prevention, and epidemiologic research. *Cancer Research* seeks manuscripts that offer pathobiological and translational impact to inform the personal, clinical, and societal problems posed by cancer. The main scope of the Journal is captured in its primary subsections, which focus on molecular and cellular pathobiology, tumor and stem cell biology, therapeutics and targets, microenvironment and immunology, prevention and epidemiology, and integrated systems and technology.

Review Article

The Four Faces of Autophagy: Implications for Cancer Therapy

David A. Gewirtz

David A. Gewirtz

Abstract

It is generally thought that autophagy has two primary and opposing functions in tumor cells in response to stress induced by chemotherapy or radiation. One is the cytoprotective function that can in theory be inhibited for therapeutic advantage by sensitizing the cells to these treatment modalities. The other is the cytotoxic function that is generally not observed with conventional treatment modalities, but that may function to promote tumor cell killing either alone or in association with apoptosis. In this commentary/review, we advance the premise that autophagy is actually populated by at least two additional players. One we have termed the nonprotective form of autophagy, where the cell is apparently carrying out autophagy-mediated degradative functions, but where autophagy inhibition does not lead to perceptible alterations in drug or radiation sensitivity. The other is what we now term the cytostatic form of autophagy in that its activation results in prolonged growth inhibition as well as reduced clonogenic survival (loss of reproductive capacity) but in the absence of actual loss of cell viability through apoptosis or necrosis; however, as is the case with cytototoxic autophagy, inhibition of cytostatic autophagy protects the tumor cell from the agent (drugs or radiation) that promotes the autophagic response. In view of current clinical efforts to exploit autophagy inhibition as a therapeutic strategy for sensitization of malignancies to chemotherapy and radiation, it is critical to recognize that if chemotherapy and/or radiation actually promote autophagy in patient tumors, the autophagy is not of necessity cytoprotective in function. *Cancer Res; 74(3); 647–51. ©2014 AACR.*

Cancer Res February 1, 2014 74:647; Published OnlineFirst January 23, 2014; doi: 10.1158/0008-5472.CAN-13-2966

Perspective

Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States

Lola Rahib, Benjamin D. Smith, Rhonda Aizenberg, Allison B. Rosenzweig, Julie M. Fleshman, and Lynn M. Matrisian

Lynn M. Matrisian

Abstract

Cancer incidence and deaths in the United States were projected for the most common cancer types for the years 2020 and 2030 based on changing demographics and the average annual percentage changes in incidence and death rates. Breast, prostate, and lung cancers will remain the top cancer diagnoses throughout this time, but thyroid cancer will replace colorectal cancer as the fourth leading cancer diagnosis by 2030, and melanoma and uterine cancer will become the fifth and sixth most common cancers, respectively. Lung cancer is projected to remain the top cancer killer throughout this time period. However, pancreas and liver cancers are projected to surpass breast, prostate, and colorectal cancers to become the second and third leading causes of cancer-related death by 2030, respectively. Advances in screening, prevention, and treatment can change cancer incidence and/or death rates, but it will require a concerted effort by the research and healthcare communities now to effect a substantial change for the future. *Cancer Res; 74(11); 2913–21. ©2014 AACR.*

Cancer Res June 1, 2014 74:2913; Published OnlineFirst May 19, 2014; doi: 10.1158/0008-5472.CAN-14-0155

Research Article

PCAT-1, a Long Noncoding RNA, Regulates BRCA2 and Controls Homologous Recombination in Cancer

John R. Prensner, Wei Chen, Matthew K. Iyer, Qi Cao, Teng Ma, Sumin Han, Anirban Sahu, Rohit Malik, Kari Wilder-Romans, Nora Navone, Christopher J. Logothetis, John C. Araujo, Louis L. Pisters, Ashutosh K. Tewari, Christine E. Canman, Karen E. Knudsen, Naoki Kitabayashi, Mark A. Rubin, Francesca Demichelis, Theodore S. Lawrence, Arul M. Chinnaiyan, and Felix Y. Feng

Arul M. Chinnaiyan

Felix Y. Feng

Abstract

Impairment of double-stranded DNA break (DSB) repair is essential to many cancers. However, although mutations in DSB repair proteins are common in hereditary cancers, mechanisms of impaired DSB repair in sporadic cancers remain incompletely understood. Here, we describe the first role for a long noncoding RNA (lncRNA) in DSB repair in prostate cancer. We identify *PCAT-1*, a prostate cancer outlier lncRNA, which regulates cell response to genotoxic stress. *PCAT-1* expression produces a functional deficiency in homologous recombination through its repression of the *BRCA2* tumor suppressor, which, in turn, imparts a high sensitivity to small-molecule inhibitors of *PARP1*. These effects reflected a posttranscriptional repression of the *BRCA2* 3′UTR by *PCAT-1*. Our observations thus offer a novel mechanism of "BRCAness" in sporadic cancers. *Cancer Res; 74(6); 1651–60. ©2014 AACR.*

Cancer Res March 15, 2014 74:1651; Published OnlineFirst January 28, 2014; doi: 10.1158/0008-5472.CAN-13-3159

Research Article

High Fidelity Patient-Derived Xenografts for Accelerating Prostate Cancer Discovery and Drug Development

Dong Lin, Alexander W. Wyatt, Hui Xue, Yuwei Wang, Xin Dong, Anne Haegert, Rebecca Wu, Sonal Brahmbhatt, Fan Mo, Lina Jong, Robert H. Bell, Shawn Anderson, Antonio Hurtado-Coll, Ladan Fazli, Manju Sharma, Himisha Beltran, Mark Rubin, Michael Cox, Peter W. Gout, James Morris, Larry Goldenberg, Stanislav V. Volik, Martin E. Gleave, Colin C. Collins, and Yuzhuo Wang

Colin C. Collins Yuzhuo Wang

Abstract

Standardized and reproducible preclinical models that recapitulate the dynamics of prostate cancer are urgently needed. We established a bank of transplantable patient-derived prostate cancer xenografts that capture the biologic and molecular heterogeneity currently confounding prognostication and therapy development. Xenografts preserved the histopathology, genome architecture, and global gene expression of donor tumors. Moreover, their aggressiveness matched patient observations, and their response to androgen withdrawal correlated with tumor subtype. The panel includes the first xenografts generated from needle biopsy tissue obtained at diagnosis. This advance was exploited to generate independent xenografts from different sites of a primary site, enabling functional dissection of tumor heterogeneity. Prolonged exposure of adenocarcinoma xenografts to androgen withdrawal led to castration-resistant prostate cancer, including the first-in-field model of complete transdifferentiation into lethal neuroendocrine prostate cancer. Further analysis of this model supports the hypothesis that neuroendocrine prostate cancer can evolve directly from adenocarcinoma via an adaptive response and yielded a set of genes potentially involved in neuroendocrine transdifferentiation. We predict that these next-generation models will be transformative for advancing mechanistic understanding of disease progression, response to therapy, and personalized oncology. *Cancer Res; 74(4); 1272–83. ©2013 AACR.*

Cancer Res February 15, 2014 74:1272; Published OnlineFirst December 19, 2013; doi: 10.1158/0008-5472.CAN-13-2921-T

Research Article

Inhibition of CSF-1 Receptor Improves the Antitumor Efficacy of Adoptive Cell Transfer Immunotherapy

Stephen Mok, Richard C. Koya, Christopher Tsui, Jingying Xu, Lídia Robert, Lily Wu, Thomas G. Graeber, Brian L. West, Gideon Bollag, and Antoni Ribas

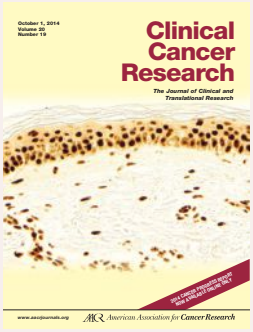
Richard C. Koya Antoni Ribas

Abstract

Colony stimulating factor 1 (CSF-1) recruits tumor-infiltrating myeloid cells (TIM) that suppress tumor immunity, including M2 macrophages and myeloid-derived suppressor cells (MDSC). The CSF-1 receptor (CSF-1R) is a tyrosine kinase that is targetable by small molecule inhibitors such as PLX3397. In this study, we used a syngeneic mouse model of *BRAF*^{V600E}-driven melanoma to evaluate the ability of PLX3397 to improve the efficacy of adoptive cell therapy (ACT). In this model, we found that combined treatment produced superior antitumor responses compared with single treatments. In mice receiving the combined treatment, a dramatic reduction of TIMs and a skewing of MHCII^{low} to MHCII^{hi} macrophages were observed. Furthermore, mice receiving the combined treatment exhibited an increase in tumor-infiltrating lymphocytes (TIL) and T cells, as revealed by real-time imaging *in vivo*. In support of these observations, TILs from these mice released higher levels of IFN-γ. In conclusion, CSF-1R blockade with PLX3397 improved the efficacy of ACT immunotherapy by inhibiting the intratumoral accumulation of immunosuppressive macrophages. *Cancer Res; 74(1); 153–61. ©2013 AACR.*

Cancer Res January 1, 2014 74:153; Published OnlineFirst November 18, 2013; doi: 10.1158/0008-5472.CAN-13-1816

Clinical Cancer Research



Kenneth C. Anderson, MD
Editor-in-Chief

Scope

Clinical Cancer Research publishes innovative clinical and translational cancer research studies that bridge the laboratory and the clinic. The Journal is especially interested in clinical trials evaluating new treatments, accompanied by research on pharmacology, and molecular alterations or biomarkers that predict response or resistance to treatment. The Journal also prioritizes laboratory and animal studies of new drugs and molecule-targeted agents with the potential to lead to clinical trials, and studies of targetable mechanisms of oncogenesis, progression of the malignant phenotype, and metastatic disease.

Review Article

Hepatocellular Carcinoma: Reasons for Phase III Failure and Novel Perspectives on Trial Design

Josep M. Llovet and Virginia Hernandez-Gea

Josep M. Llovet

Abstract

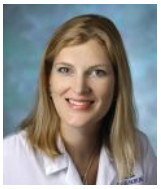
Hepatocellular carcinoma (HCC) is a major health problem. Most patients with HCC experience a recurrence after resection/ablation or are diagnosed at advanced stages. Sorafenib remains the only approved systemic drug for these patients. Molecular therapies targeting signaling cascades involved in hepatocarcinogenesis have been explored in phase III clinical trials. However, none of the drugs tested have shown positive results in the first-line (brivanib, sunitinib, erlotinib, and linifanib) or second-line (brivanib, everolimus) setting after sorafenib progression. Reasons for failure are heterogeneous and include lack of understanding of critical drivers of tumor progression/dissemination, liver toxicity, flaws in trial design, or marginal antitumoral potency. These trials are also challenging time to progression as a surrogate endpoint of survival. Trials ongoing testing drugs head-to-head versus sorafenib in "all comers" might have difficulties in achieving superior results in the first line. Novel trials are also designed testing drugs in biomarker-based subpopulations of patients with HCC. Most common mutations, however, are undruggable, such as *p53* and *CTNNB1*. Two types of studies are proposed: (i) phase II pivotal proof-of-concept studies testing drugs blocking potential oncogenic addiction loops, such as the one testing MEK inhibitors in RAS^{+} patients or amplification of *FGF19* as a target; and (ii) phase II to III studies using biomarker-based trial enrichment for defining HCC subpopulations, such as the case of enriching for *MET*-positive tumors. These strategies have been deemed successful in breast, melanoma, and lung cancers, and are expected to change the landscape of trial design of HCC. *Clin Cancer Res; 20(8); 2072–9.*

Clin Cancer Res April 15, 2014 20:2072; Published OnlineFirst March 3, 2014; doi: 10.1158/1078-0432.CCR-13-0547

Research Article

Association of PD-1, PD-1 Ligands, and Other Features of the Tumor Immune Microenvironment with Response to Anti–PD-1 Therapy


Suzanne L. Topalian


Janis M. Taube

Janis M. Taube, Alison Klein, Julie R. Brahmer, Haiying Xu, Xiaoyu Pan, Jung H. Kim, Lieping Chen, Drew M. Pardoll, Suzanne L. Topalian, and Robert A. Anders

Abstract

Purpose: Immunomodulatory drugs differ in mechanism-of-action from directly cytotoxic cancer therapies. Identifying factors predicting clinical response could guide patient selection and therapeutic optimization.

Experimental Design: Patients ($N = 41$) with melanoma, non–small cell lung carcinoma (NSCLC), renal cell carcinoma (RCC), colorectal carcinoma, or castration-resistant prostate cancer were treated on an early-phase trial of anti–PD-1 (nivolumab) at one institution and had evaluable pretreatment tumor specimens. Immunoarchitectural features, including PD-1, PD-L1, and PD-L2 expression, patterns of immune cell infiltration, and lymphocyte subpopulations, were assessed for interrelationships and potential correlations with clinical outcomes.

Results: Membranous (cell surface) PD-L1 expression by tumor cells and immune infiltrates varied significantly by tumor type and was most abundant in melanoma, NSCLC, and RCC. In the overall cohort, PD-L1 expression was geographically associated with infiltrating immune cells ($P < 0.001$), although lymphocyte-rich regions were not always associated with PD-L1 expression. Expression of PD-L1 by tumor cells and immune infiltrates was significantly associated with expression of PD-1 on lymphocytes. PD-L2, the second ligand for PD-1, was associated with PD-L1 expression. Tumor cell PD-L1 expression correlated with objective response to anti–PD-1 therapy, when analyzing either the specimen obtained closest to therapy or the highest scoring sample among multiple biopsies from individual patients. These correlations were stronger than borderline associations of PD-1 expression or the presence of intratumoral immune cell infiltrates with response.

Conclusions: Tumor PD-L1 expression reflects an immune-active microenvironment and, while associated other immunosuppressive molecules, including PD-1 and PD-L2, is the single factor most closely correlated with response to anti–PD-1 blockade. *Clin Cancer Res; 20(19); 5064–74. ©2014 AACR.*

Clin Cancer Res October 1, 2014 20:5064; Published OnlineFirst April 8, 2014; doi: 10.1158/1078-0432.CCR-13-3271

Research Article

Noninvasive Detection of Response and Resistance in *EGFR*-Mutant Lung Cancer Using Quantitative Next-Generation Genotyping of Cell-Free Plasma DNA


Geoffrey R. Oxnard

Geoffrey R. Oxnard, Cloud P. Paweletz, Yanan Kuang, Stacy L. Mach, Allison O'Connell, Melissa M. Messineo, Jason J. Luke, Mohit Butaney, Paul Kirschmeier, David M. Jackman, and Pasi A. Jänne

Abstract

Purpose: Tumor genotyping using cell-free plasma DNA (cfDNA) has the potential to allow noninvasive assessment of tumor biology, yet many existing assays are cumbersome and vulnerable to false-positive results. We sought to determine whether droplet digital PCR (ddPCR) of cfDNA would allow highly specific and quantitative assessment of tumor genotype.

Experimental Design: ddPCR assays for *EGFR*, *KRAS*, and *BRAF* mutations were developed using plasma collected from patients with advanced lung cancer or melanoma of a known tumor genotype. Sensitivity and specificity were determined using cancers with nonoverlapping genotypes as positive and negative controls. Serial assessment of response and resistance was studied in patients with *EGFR*-mutant lung cancer on a prospective trial of erlotinib.

Results: We identified a reference range for *EGFR* L858R and exon 19 deletions in specimens from *KRAS*-mutant lung cancer, allowing identification of candidate thresholds with high sensitivity and 100% specificity. Received operative characteristic curve analysis of four assays demonstrated an area under the curve in the range of 0.80 to 0.94. Sensitivity improved in specimens with optimal cfDNA concentrations. Serial plasma genotyping of *EGFR*-mutant lung cancer on erlotinib demonstrated pretreatment detection of *EGFR* mutations, complete plasma response in most cases, and increasing levels of *EGFR* T790M emerging before objective progression.

Conclusions: Noninvasive genotyping of cfDNA using ddPCR demonstrates assay qualities that could allow effective translation into a clinical diagnostic. Serial quantification of plasma genotype allows noninvasive assessment of response and resistance, including detection of resistance mutations up to 16 weeks before radiographic progression. *Clin Cancer Res; 20(6); 1698–705. ©2014 AACR.*

Clin Cancer Res March 15, 2014 20:1698; Published OnlineFirst January 15, 2014; doi: 10.1158/1078-0432.CCR-13-2482

Research Article

Emergence of Constitutively Active Estrogen Receptor-α Mutations in Pretreated Advanced Estrogen Receptor–Positive Breast Cancer


Myles Brown

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Abstract

Purpose: We undertook this study to determine the prevalence of estrogen receptor (ER) α (*ESR1*) mutations throughout the natural history of hormone-dependent breast cancer and to delineate the functional roles of the most commonly detected alterations.

Experimental Design: We studied a total of 249 tumor specimens from 208 patients. The specimens include 134 ER-positive (ER^+/$HER2^-$) and, as controls, 115 ER-negative (ER^-) tumors. The ER^+ samples consist of 58 primary breast cancers and 76 metastatic samples. All tumors were sequenced to high unique coverage using next-generation sequencing targeting the coding sequence of the estrogen receptor and an additional 182 cancer-related genes.

Results: Recurring somatic mutations in codons 537 and 538 within the ligand-binding domain of ER were detected in ER^+ metastatic disease. Overall, the frequency of these mutations was 12% [9/76; 95% confidence interval (CI), 6%–21%] in metastatic tumors and in a subgroup of patients who received an average of 7 lines of treatment the frequency was 20% (5/25; 95% CI, 7%–41%). These mutations were not detected in primary or treatment-naïve ER^+ cancer or in any stage of ER^- disease. Functional studies in cell line models demonstrate that these mutations render estrogen receptor constitutive activity and confer partial resistance to currently available endocrine treatments.

Conclusions: In this study, we show evidence for the temporal selection of functional *ESR1* mutations as potential drivers of endocrine resistance during the progression of ER^+ breast cancer. *Clin Cancer Res; 20(7); 1757–67. ©2014 AACR.*

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Research Article

Germline and Somatic Mutations in Homologous Recombination Genes Predict Platinum Response and Survival in Ovarian, Fallopian Tube, and Peritoneal Carcinomas


Elizabeth M. Swisher

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Abstract

Purpose: Hallmarks of germline *BRCA1/2*-associated ovarian carcinomas include chemosensitivity and improved survival. The therapeutic impact of somatic *BRCA1/2* mutations and mutations in other homologous recombination DNA repair genes is uncertain.

Experimental Design: Using targeted capture and massively parallel genomic sequencing, we assessed 390 ovarian carcinomas for germline and somatic loss-of-function mutations in 30 genes, including *BRCA1*, *BRCA2*, and 11 other genes in the homologous recombination pathway.

Results: Thirty-one percent of ovarian carcinomas had a deleterious germline (24%) and/or somatic (9%) mutation in one or more of the 13 homologous recombination genes: *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CHEK1*, *CHEK2*, *FAM175A*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*, and *RAD51D*. Nonserous ovarian carcinomas had similar rates of homologous recombination mutations to serous carcinomas (28% vs. 31%, $P = 0.6$), including clear cell, endometrioid, and carcinosarcoma. The presence of germline and somatic homologous recombination mutations was highly predictive of primary platinum sensitivity ($P = 0.0002$) and improved overall survival ($P = 0.0006$), with a median overall survival of 66 months in germline homologous recombination mutation carriers, 59 months in cases with a somatic homologous recombination mutation, and 41 months for cases without a homologous recombination mutation.

Conclusions: Germline or somatic mutations in homologous recombination genes are present in almost one third of ovarian carcinomas, including both serous and nonserous histologies. Somatic *BRCA1/2* mutations and mutations in other homologous recombination genes have a similar positive impact on overall survival and platinum responsiveness as germline *BRCA1/2* mutations. The similar rate of homologous recombination mutations in nonserous carcinomas supports their inclusion in PARP inhibitor clinical trials. *Clin Cancer Res; 20(3); 764–75. ©2013 AACR.*

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Molecular Cancer Research

Karen E. Knudsen, PhD
Editor-in-Chief

Scope

Molecular Cancer Research publishes articles describing novel basic cancer research discoveries of broad interest to the field. Studies must be of demonstrated significance, and the Journal prioritizes analyses performed at the molecular and cellular level that reveal novel mechanistic insight into pathways and processes linked to cancer risk, development, and/or progression. Areas of emphasis include all cancer-associated pathways (including cell-cycle regulation; cell death; chromatin regulation; DNA damage and repair; gene and RNA regulation; genomics; oncogenes and tumor suppressors; and signal transduction), in addition to studies describing new molecular mechanisms and interactions that support cancer phenotypes.

Review Article

Nicotine-Mediated Cell Proliferation and Tumor Progression in Smoking-Related Cancers

Courtney Schaal and Srikumar P. Chellappan

Srikumar P. Chellappan

Abstract

Tobacco smoke contains multiple classes of established carcinogens including benzo(*a*)pyrenes, polycyclic aromatic hydrocarbons, and tobacco-specific nitrosamines. Most of these compounds exert their genotoxic effects by forming DNA adducts and generation of reactive oxygen species, causing mutations in vital genes such as K-Ras and p53. In addition, tobacco-specific nitrosamines can activate nicotinic acetylcholine receptors (nAChR) and to a certain extent β-adrenergic receptors (β-AR), promoting cell proliferation. Furthermore, it has been demonstrated that nicotine, the major addictive component of tobacco smoke, can induce cell-cycle progression, angiogenesis, and metastasis of lung and pancreatic cancers. These effects occur mainly through the α7-nAChRs, with possible contribution from the β-ARs and/or epidermal growth factor receptors. This review article will discuss the molecular mechanisms by which nicotine and its oncogenic derivatives such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and N-nitrosonornicotine induce cell-cycle progression and promote tumor growth. A variety of signaling cascades are induced by nicotine through nAChRs, including the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway, phosphoinositide 3-kinase/AKT pathway, and janus-activated kinase/STAT signaling. In addition, studies have shown that nAChR activation induces Src kinase in a β-arrestin-1-dependent manner, leading to the inactivation of Rb protein and resulting in the expression of E2F1-regulated proliferative genes. Such nAChR-mediated signaling events enhance the proliferation of cells and render them resistant to apoptosis induced by various agents. These observations highlight the role of nAChRs in promoting the growth and metastasis of tumors and raise the possibility of targeting them for cancer therapy. *Mol Cancer Res; 12(1); 14–23. ©2014 AACR.*

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Research Article

Mutational Landscape of the Essential Autophagy Gene *BECN1* in Human Cancers

Saurabh V. Laddha, Shridar Ganesan, Chang S. Chan, and Eileen White


Eileen White


Chang S. Chan

Abstract

Evidence suggests that the catabolic process of macroautophagy (autophagy hereafter) can either suppress or promote cancer. The essential autophagy gene *ATG6/BECN1* encoding the Beclin1 protein has been implicated as a haploinsufficient tumor suppressor in breast, ovarian, and prostate cancers. The proximity of *BECN1* to the known breast and ovarian tumor suppressor breast cancer 1, early onset, *BRCA1*, on chromosome 17q21, has made this determination equivocal. Here, the mutational status of *BECN1* was assessed in human tumor sequencing data from The Cancer Genome Atlas (TCGA) and other databases. Large deletions encompassing both *BRCA1* and *BECN1*, and deletions of only *BRCA1* but not *BECN1*, were found in breast and ovarian cancers, consistent with *BRCA1* loss being a primary driver mutation in these cancers. Furthermore, there was no evidence for *BECN1* mutation or loss in any other cancer, casting doubt on whether *BECN1* is a tumor suppressor in most human cancers.

Implications: Contrary to previous reports, *BECN1* is not significantly mutated in human cancer and not a tumor-suppressor gene, as originally thought.

Visual Overview: http://mcr.aacrjournals.org/content/early/2014/04/01/1541-7786.MCR-13-0614/F1.large.jpg. *Mol Cancer Res; 12(4); 485–90. ©2014 AACR.*

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Research Article

MiR-335 Inhibits Small Cell Lung Cancer Bone Metastases via IGF-IR and RANKL Pathways

Meng Gong, Junrong Ma, Ryan Guillemette, Mingliang Zhou, Yan Yang, Yujing Yang, Janet M. Hock, and Xijie Yu


Xijie Yu

Abstract

Small cell lung cancer (SCLC) is a rapidly progressing, incurable cancer that frequently spreads to bone. New insights are needed to identify therapeutic targets to prevent or retard SCLC metastatic progression. Human SCLC SBC-5 cells in mouse xenograft models home to skeletal and nonskeletal sites, whereas human SCLC SBC-3 cells only pervade nonskeletal sites. Because microRNAs (miRNA) often act as tumor regulators, we investigated their role in preclinical models of SCLC. miRNA expression profiling revealed selective and reduced expression of miRNA (miR)-335 and miR-29a in SBC-5 cells, compared with SBC-3 cells. In SBC-5 cells, miR-335 expression correlated with bone osteolytic lesions, whereas miR-29a expression did not. Overexpression of miR-335 in SBC-5 cells significantly reduced cell migration, invasion, proliferation, colony formation, and osteoclast induction *in vitro*. Importantly, in miR-335 overexpressing SBC-5 cell xenografts ($n = 10$), there were minimal osteolytic lesions in the majority of mice and none in three mice. Expression of RANK ligand (RANKL) and insulin-like growth factor-I receptor (IGF-IR), key mediators of bone metastases, were elevated in SBC-5 as compared with SBC-3 cells. Mechanistically, overexpression of miR-335 in SBC-5 cells reduced RANKL and IGF-IR expression. In conclusion, loss of miR-335 promoted SCLC metastatic skeletal lesions via deregulation of IGF-IR and RANKL pathways and was associated with metastatic osteolytic skeletal lesions.

Implications: These preclinical findings establish a need to pursue the role of miR-335 in human SCLC with metastatic skeletal disease. *Mol Cancer Res; 12(1); 101–10. 2013 AACR.*

Mol Cancer Res January 2014 12:101; Published OnlineFirst August 21, 2013; doi: 10.1158/1541-7786.MCR-13-0136

Research Article

CXCR4, but not CXCR7, Discriminates Metastatic Behavior in Non–Small Cell Lung Cancer Cells

Young H. Choi, Marie D. Burdick, Brett A. Strieter, Borna Mehrad, and Robert M. Strieter

Robert M. Strieter

Abstract

Chemokines have been implicated as key contributors of non–small cell lung cancer (NSCLC) metastasis. However, the role of CXCR7, a recently discovered receptor for CXCL12 ligand, in the pathogenesis of NSCLC is unknown. To define the relative contribution of chemokine receptors to migration and metastasis, we generated human lung A549 and H157 cell lines with stable knockdown of CXCR4, CXCR7, or both. Cancer cells exhibited chemotaxis to CXCL12 that was enhanced under hypoxic conditions, associated with a parallel induction of CXCR4, but not CXCR7. Interestingly, neither knockdown cell line differed in the rate of proliferation, apoptosis, or cell adherence; however, in both cell lines, CXCL12-induced migration was abolished when CXCR4 signaling was abrogated. In contrast, inhibition of CXCR7 signaling did not alter cellular migration to CXCL12. In an *in vivo* heterotropic xenograft model using A549 cells, expression of CXCR4, but not CXCR7, on cancer cells was necessary for the development of metastases. In addition, cancer cells knocked down for CXCR4 (or both CXCR4 and CXCR7) produced larger and more vascular tumors as compared with wild-type or CXCR7 knockdown tumors, an effect that was attributable to cancer cell–derived CXCR4 out competing endothelial cells for available CXCL12 in the tumor microenvironment. These results indicate that CXCR4, not CXCR7, expression engages CXCL12 to mediate NSCLC metastatic behavior.

Implications: Targeting CXCR4-mediated migration and metastasis may be a viable therapeutic option in NSCLC. *Mol Cancer Res; 12(1); 38–47. ©2013 AACR.*

Mol Cancer Res January 2014 12:38; Published OnlineFirst September 11, 2013 doi: 10.1158/1541-7786.MCR-12-0334

Research Article

ROS1 and *ALK* Fusions in Colorectal Cancer, with Evidence of Intratumoral Heterogeneity for Molecular Drivers

Dara L. Aisner, Teresa T. Nguyen, Diego D. Paskulin, Anh T. Le, Jerry Haney, Nathan Schulte, Fiona Chionh, Jenny Hardingham, John Mariadason, Niall Tebbutt, Robert C. Doebele, Andrew J. Weickhardt, and Marileila Varella-Garcia

Marileila Varella-Garcia

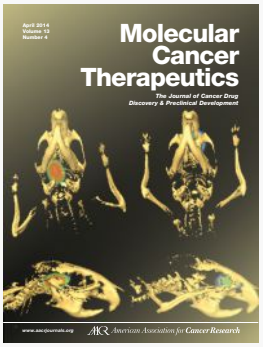
Abstract

Activated anaplastic lymphoma kinase (*ALK)* and *ROS1* tyrosine kinases, through gene fusions, have been found in lung adenocarcinomas and are highly sensitive to selective kinase inhibitors. This study aimed at identifying the presence of these rearrangements in human colorectal adenocarcinoma specimens using a 4-target, 4-color break-apart FISH assay to simultaneously determine the genomic status of *ALK* and *ROS1*. Among the clinical colorectal cancer specimens analyzed, rearrangement-positive cases for both *ALK* and *ROS1* were observed. The fusion partner for *ALK* was identified as *EML4* and the fusion partner for one of the *ROS1*-positive cases was *SLC34A2*, the partner for the other *ROS1*-positive case remains to be identified. A small fraction of specimens presented duplicated or clustered copies of native *ALK* and *ROS1*. In addition, rearrangements were detected in samples that also harbored *KRAS* and *BRAF* mutations in two of the three cases. Interestingly, the *ALK*-positive specimen displayed marked intratumoral heterogeneity and rearrangement was also identified in regions of high-grade dysplasia. Despite the additional oncogenic events and tumor heterogeneity observed, elucidation of the first cases of *ROS1* rearrangements and confirmation of *ALK* rearrangements support further evaluation of these genomic fusions as potential therapeutic targets in colorectal cancer.

Implications: *ROS1* and *ALK* fusions occur in colorectal cancer and may have substantial impact in therapy selection. *Mol Cancer Res; 12(1); 111–8. ©2013 AACR.*

Mol Cancer Res January 2014 12:111; Published OnlineFirst December 2, 2013 doi: 10.1158/1541-7786.MCR-13-0479-T

Molecular Cancer Therapeutics



Napoleone Ferrara, MD
Editor-in-Chief

Scope

Molecular Cancer Therapeutics strives to be the top choice for publishing the best science in the discovery and preclinical development of novel therapeutic agents for oncology, preclinical studies of approved therapeutics, mechanisms of drug action, mechanisms of drug resistance, biomarkers of drug response, novel models and technologies, and occasional drug toxicity mechanisms. While the Journal's main focus is on small molecule and protein drugs, other molecular entities may be considered.

Review Article

Picking the Point of Inhibition: A Comparative Review of PI3K/AKT/mTOR Pathway Inhibitors

Rodrigo Dienstmann, Jordi Rodon, Violeta Serra, and Josep Tabernero

Rodrigo Dienstmann

Abstract

The frequent activation of the PI3K/AKT/mTOR pathway in cancer, and its crucial role in cell growth and survival, has made it a much desired target for pharmacologic intervention. Following the regulatory approval of the rapamycin analogs everolimus and temsirolimus, recent years have seen an explosion in the number of phosphoinositide 3-kinase (PI3K) pathway inhibitors under clinical investigation. These include: ATP-competitive, dual inhibitors of class I PI3K and mTORC1/2; "pan-PI3K" inhibitors, which inhibit all four isoforms of class I PI3K (α, β, δ, γ); isoform-specific inhibitors of the various PI3K isoforms; allosteric and catalytic inhibitors of AKT; and ATP-competitive inhibitors of mTOR only (and thus mTORC1 and mTORC2). With so many agents in development, clinicians are currently faced with a wide array of clinical trials investigating a multitude of inhibitors with different mechanisms of action, being used both as single agents and in combination with other therapies. Here, we provide a review of the literature, with the aim of differentiating the genomic contexts in which these various types of inhibitors may potentially have superior activity. *Mol Cancer Ther; 13(5); 1021–31. ©2014 AACR.*

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Research Article

Selective Inhibition of EZH2 by EPZ-6438 Leads to Potent Antitumor Activity in *EZH2*-Mutant Non-Hodgkin Lymphoma


Heike Keilhack


Akira Yokoi

Sarah K. Knutson, Satoshi Kawano, Yukinori Minoshima, Natalie M. Warholic, Kuan-Chun Huang, Yonghong Xiao, Tadashi Kadowaki, Mai Uesugi, Galina Kuznetsov, Namita Kumar, Tim J. Wigle, Christine R. Klaus, Christina J. Allain, Alejandra Raimondi, Nigel J. Waters, Jesse J. Smith, Margaret Porter-Scott, Richard Chesworth, Mikel P. Moyer, Robert A. Copeland, Victoria M. Richon, Toshimitsu Uenaka, Roy M. Pollock, Kevin W. Kuntz, Akira Yokoi, and Heike Keilhack

Abstract

Mutations within the catalytic domain of the histone methyltransferase EZH2 have been identified in subsets of patients with non-Hodgkin lymphoma (NHL). These genetic alterations are hypothesized to confer an oncogenic dependency on EZH2 enzymatic activity in these cancers. We have previously reported the discovery of EPZ005678 and EPZ-6438, potent and selective *S*-adenosyl-methionine-competitive small molecule inhibitors of EZH2. Although both compounds are similar with respect to their mechanism of action and selectivity, EPZ-6438 possesses superior potency and drug-like properties, including good oral bioavailability in animals. Here, we characterize the activity of EPZ-6438 in preclinical models of NHL. EPZ-6438 selectively inhibits intracellular lysine 27 of histone H3 (H3K27) methylation in a concentration- and time-dependent manner in both *EZH2* wild-type and mutant lymphoma cells. Inhibition of H3K27 trimethylation (H3K27Me3) leads to selective cell killing of human lymphoma cell lines bearing EZH2 catalytic domain point mutations. Treatment of *EZH2*-mutant NHL xenograft-bearing mice with EPZ-6438 causes dose-dependent tumor growth inhibition, including complete and sustained tumor regressions with correlative diminution of H3K27Me3 levels in tumors and selected normal tissues. Mice dosed orally with EPZ-6438 for 28 days remained tumor free for up to 63 days after stopping compound treatment in two *EZH2*-mutant xenograft models. These data confirm the dependency of *EZH2*-mutant NHL on EZH2 activity and portend the utility of EPZ-6438 as a potential treatment for these genetically defined cancers. *Mol Cancer Ther; 13(4); 842–54. ©2014 AACR.*

Mol Cancer Ther April 2014 13:842; Published OnlineFirst February 21, 2014; doi: 10.1158/1535-7163.MCT-13-0773

Research Article

Stereospecific PARP Trapping by BMN 673 and Comparison with Olaparib and Rucaparib


Yves Pommier

Junko Murai, Shar-Yin N. Huang, Amèlie Renaud, Yiping Zhang, Jiuping Ji, Shunichi Takeda, Joel Morris, Beverly Teicher, James H. Doroshow, and Yves Pommier

Abstract

Anti-PARP drugs were initially developed as catalytic inhibitors to block the repair of DNA single-strand breaks. We recently reported that several PARP inhibitors have an additional cytotoxic mechanism by trapping PARP–DNA complexes, and that both olaparib and niraparib act as PARP poisons at pharmacologic concentrations. Therefore, we have proposed that PARP inhibitors should be evaluated based both on catalytic PARP inhibition and PARP–DNA trapping. Here, we evaluated the novel PARP inhibitor, BMN 673, and compared its effects on PARP1 and PARP2 with two other clinical PARP inhibitors, olaparib and rucaparib, using biochemical and cellular assays in genetically modified chicken DT40 and human cancer cell lines. Although BMN 673, olaparib, and rucaparib are comparable at inhibiting PARP catalytic activity, BMN 673 is ~100-fold more potent at trapping PARP–DNA complexes and more cytotoxic as single agent than olaparib, whereas olaparib and rucaparib show similar potencies in trapping PARP–DNA complexes. The high level of resistance of PARP1/2 knockout cells to BMN 673 demonstrates the selectivity of BMN 673 for PARP1/2. Moreover, we show that BMN 673 acts by stereospecific binding to PARP1 as its enantiomer, LT674, is several orders of magnitude less efficient. BMN 673 is also approximately 100-fold more cytotoxic than olaparib and rucaparib in combination with the DNA alkylating agents methyl methane sulfonate (MMS) and temozolomide. Our study demonstrates that BMN 673 is the most potent clinical PARP inhibitor tested to date with the highest efficiency at trapping PARP–DNA complexes. *Mol Cancer Ther; 13(2); 433–43. ©2013 AACR.*

Mol Cancer Ther February 2014 13:433; Published OnlineFirst December 19, 2013; doi: 10.1158/1535-7163.MCT-13-0803

Research Article

Characterization of the Novel and Specific PI3Kα Inhibitor NVP-BYL719 and Development of the Patient Stratification Strategy for Clinical Trials


Christine Fritsch

Christine Fritsch, Alan Huang, Christian Chatenay-Rivauday, Christian Schnell, Anupama Reddy, Manway Liu, Audrey Kauffmann, Daniel Guthy, Dirk Erdmann, Alain De Pover, Pascal Furet, Hui Gao, Stephane Ferretti, Youzhen Wang, Joerg Trappe, Saskia M. Brachmann, Sauveur-Michel Maira, Christopher Wilson, Markus Boehm, Carlos Garcia-Echeverria, Patrick Chene, Marion Wiesmann, Robert Cozens, Joseph Lehar, Robert Schlegel, Giorgio Caravatti, Francesco Hofmann, and William R. Sellers

Abstract

Somatic *PIK3CA* mutations are frequently found in solid tumors, raising the hypothesis that selective inhibition of PI3Kα may have robust efficacy in *PIK3CA*-mutant cancers while sparing patients the side-effects associated with broader inhibition of the class I phosphoinositide 3-kinase (PI3K) family. Here, we report the biologic properties of the 2-aminothiazole derivative NVP-BYL719, a selective inhibitor of PI3Kα and its most common oncogenic mutant forms. The compound selectivity combined with excellent drug-like properties translates to dose- and time-dependent inhibition of PI3Kα signaling *in vivo*, resulting in robust therapeutic efficacy and tolerability in *PIK3CA*-dependent tumors. Novel targeted therapeutics such as NVP-BYL719, designed to modulate aberrant functions elicited by cancer-specific genetic alterations upon which the disease depends, require well-defined patient stratification strategies in order to maximize their therapeutic impact and benefit for the patients. Here, we also describe the application of the Cancer Cell Line Encyclopedia as a preclinical platform to refine the patient stratification strategy for NVP-BYL719 and found that *PIK3CA* mutation was the foremost positive predictor of sensitivity while revealing additional positive and negative associations such as *PIK3CA* amplification and *PTEN* mutation, respectively. These patient selection determinants are being assayed in the ongoing NVP-BYL719 clinical trials. *Mol Cancer Ther; 13(5); 1117–29. ©2014 AACR.*

Mol Cancer Ther May 2014 13:1117; Published OnlineFirst March 7, 2014; doi: 10.1158/1535-7163.MCT-13-0865

Research Article

MiR-134/487b/655 Cluster Regulates TGF-β–Induced Epithelial–Mesenchymal Transition and Drug Resistance to Gefitinib by Targeting *MAGI2* in Lung Adenocarcinoma Cells

Kazuhiro Kitamura, Masahiro Seike, Tetsuya Okano, Kuniko Matsuda, Akihiko Miyanaga, Hideaki Mizutani, Rintaro Noro, Yuji Minegishi, Kaoru Kubota, and Akihiko Gemma

Abstract

Epithelial–mesenchymal transition (EMT) has recently been recognized as a key element of cell invasion, migration, metastasis, and drug resistance in several types of cancer, including non–small cell lung cancer (NSCLC). Our aim was to clarify microRNA (miRNA)-related mechanisms underlying EMT followed by acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) in NSCLC. miRNA expression profiles were examined before and after transforming growth factor β1 (TGF-β1) exposure in four human adenocarcinoma cell lines with or without EMT. Correlation between expressions of EMT-related miRNAs and resistance to EGFR-TKI gefitinib was evaluated. miRNA array and real-time quantitative reverse transcription PCR (qRT-PCR) revealed that TGF-β1 significantly induced overexpression of miR-134, miR-487b, and miR-655, which belong to the same cluster located on chromosome 14q32, in lung adenocarcinoma cells with EMT. *MAGI2* (membrane-associated guanylate kinase, WW, and PDZ domain–containing protein 2), a predicted target of these miRNAs and a scaffold protein required for PTEN, was diminished in A549 cells with EMT after the TGF-β1 stimulation. Overexpression of miR-134 and miR-487b promoted the EMT phenomenon and affected the drug resistance to gefitinib, whereas knockdown of these miRNAs inhibited the EMT process and reversed TGF-β1–induced resistance to gefitinib. Our study demonstrated that the miR-134/487b/655 cluster contributed to the TGF-β1–induced EMT phenomenon and affected the resistance to gefitinib by directly targeting *MAGI2*, in which suppression subsequently caused loss of PTEN stability in lung cancer cells. The miR-134/miR-487b/miR-655 cluster may be a new therapeutic target in patients with advanced lung adenocarcinoma, depending on the EMT phenomenon. *Mol Cancer Ther; 13(2); 444–53. ©2013 AACR.*

Mol Cancer Ther February 2014 13:444; Published OnlineFirst November 20, 2013; doi: 10.1158/1535-7163.MCT-13-0448

In soft tissue sarcoma, where does the stroma end and the tumor begin?

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